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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,404	02/13/2004	Roger K. Sunahara	UM-08794	7762

7590 03/09/2006

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EXAMINER	
GEBREYESUS, KAGNEW H	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,404	SUNAHARA ET AL.	
	Examiner	Art Unit	
	Kagnew H. Gebreyesus	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Applicant's response on February 13, 2006 to the Office Action mailed on November 8, 2005 is acknowledged. Claims 1, 12, 13 and 14 have been amended. Claim 2 is cancelled, 16-20 remain cancelled. Claims 1, 3-15 are presently under consideration.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/13/06 has been entered.

Maintain - Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10 is rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The rejection was explained in the previous Office Action.

Applicants argue: "' ... as the Examiner has stated "the modulation identified has no real world use beyond studying the properties of the mutant cyclase enzyme itself...." (Office Action, pg. 3). Such a use provides a valid utility for the enzyme. For example, identification of compounds that alter the activity of the mutant, but not the wild type enzyme, find use in the study of substrate specificity and structure of the wild type enzyme. Such information is useful in drug design and diagnostic assays.

Applicant's argument has been carefully considered but the argument has not been found persuasive. With regards to substantial utility MPEP 2107.01 (I) B states the following:

A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

(A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;
(B) A method of treating an unspecified disease or condition;
(C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility;
(D) A method of making a material that itself has no specific, substantial, and credible utility; and
(E) A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility.

Studying the property of the mutant cyclase enzyme itself does not substantiate patentable utility as indicated in item *(A)* above. In addition applicants have neither identified any potential agent by a screening method that utilizes the mutant cyclase enzyme nor have they substantiated the

utility for any substance identified by said screening method. Therefor the rejection under 35 U.S.C. 101 is maintained.

Withdrawn - Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 12-14 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection was explained in the previous Office Action. This rejection has been withdrawn following the amendment to the claims.

Withdrawn - Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1 and 4-15 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claim 1 has been amended to include a control reaction (a reaction without the test compound) Therefore this rejection has been withdrawn.

Maintained - Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5, 6 and 14 remain rejected under 35 U.S.C. 102(a) as being anticipated by Gille et al. (Gille et a1. 2'(3')-o-(N-Methylanthraniloyl)-substituted GTP Analogs: A Novel Class of Potent Competitive Adenylyl Cyclase Inhibitors. Journal of Biological Sciences Vol. 278, No15, pp12672-12679) which first appeared on line on February 3rd, 2003). The explanation was given in the previous Office Action.

Applicants argue: " ... As described above, the claims have been amended to include the element of comprising the level of fluorescence in the presence of the test compound with the level in the absence of the test compound. In particular, Gille does not teach the claim elements of measuring the level of fluorescence of said fluorescently labeled substrate or comparing said level of fluorescence of said fluorescently labeled substrate in the presence of said test compound to the level of said fluorescence in the absence of the test compound....".

Applicant's argument has been considered but not found persuasive. Applicants argument that the assay was not done in the presence or absence of the test compound is not persuasive because Gille et al's assay reaction contained increasing concentrations of the test compound wherein the assay condition is performed with increasing concentrations of the test compound therefore the initial time point the concentration of test compound is equivalent to an assay condition where the test compound was not added i.e. without a test compound (see fig. 5).

Maintained - Claim Rejections - 35 USC § 103

Claims 1-9, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et. al (US 2002/0064849 A1) in view of Gilles et al. ("MANT-substituted guanine nucleotides: A novel class of potent adenylyl cyclase inhibitors", Life Sciences 74, 271-279 (2003).

Applicants argue "...The Examiner has rejected Claims 1-9 and 11-15 under 35 U.S.C. 103(a) as allegedly being obvious in light of Herr in view of Gille (Office Action, pg. 8). The Applicants respectfully disagree and submit that the combination of references cited by the Examiner does not teach all of the elements of the claims as required for rejection under 35 U.S.C. 103. In particular, the Applicants submit that neither Gille nor Hem alone or in combination, teach the claim elements of measuring the level of fluorescence of a fluorescent nucleotide cyclase substrate. Nor do Gill or Herr alone or in combination, teach the claim element of comparing the

level of fluorescence in the presence of the test compound with the level in the absence of the test compound. As such, the Applicants submit that the Examiner has not demonstrated a prima facie case of obviousness and respectfully request that the rejection be withdrawn."

However as indicated above, Gille et al's assay reaction contained increasing concentrations of the test compound where the initial time point of the assay condition comprises no test compound, therefore claims 1-9, 11-15 are obvious over Herr et. al in view of Gilles et al. further in view of McEwen et. al.

Claims 1-7,11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et. al (US 2002/0064849 A1) in view of Rossomando et al. further in view of McEwen et. al. This rejection maintained.

Applicants argue:" Applicants have amended Claim 1 to refer to the measurement of fluorescence over time. Unlike the present invention, which provides a real time fluorescence assay that requires no additional purification steps prior to fluorescence detection (See e.g., Examples 1-5 of the present specification), the assay of Rossomando is an end point assay that requires a purification step prior to analysis (See e.g., Rossomando, pg. 2279, column 1, experimental procedures, "Assay for Adenylate Cyclase Activity"). As such, the Applicants submit that neither Herr or Rossomando nor McEwen, alone or in combination, teach all of the elements of the claims as required for rejection under 35 U.S.C. 103 (a) and respectfully request that the rejection be withdrawn".

Applicant's argument has been fully considered but not found persuasive. However as stated in the previous Office Action, McEwen et. al teach real time measurement of nucleotide binding to G proteins using fluorescent BODIPY- GTPγS to study the kinetics of receptor-mediated and ligand induced guanine nucleotide exchange in vitro therefore given that this rejection was not made under 102 (a or b), the additional limitation to claim 1-7, 11-15 is still obvious over the combination of teachings by Herr et. al (US 2002/0064849 A1) in view of Gilles et al. further in view of McEwen et. al. as explained below.

As explained in the previous Office Action, the motivation for using a fluorescent nucleotide analogue and fluorometry in a nucleotide cyclase reaction is clearly stated in Rossomando et al. in combination with the teachings of McEwen et. al who teaches real time measurement of nucleotide binding to G proteins using fluorescent BODIPY- GTPγS to examine the kinetics of receptor-mediated and ligand induced guanine nucleotide exchange in vitro. The combination of Rossomando et al and McEwen et. al would motivate one of ordinary skill in the art to practice the invention as claimed in claims 1-7,11-15 of the instant application.

In addition applicant is reminded that this is not a 102 (a or b) type rejection. The combination of teaching by Herr et. al (US 2002/0064849 A1) in view of McEwen et. al. of claims 1-7,11-15 is an obvious type rejection.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-9, 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rammers et al in view of Holtwick et al. Rammers et al teach the use of fluorescent guanine nucleotide analogues to study G protein activation, specifically they teach the effect of a compound (mastoparan) on G proteins using MANT-GTP fluorescence kinetics. Rammers et al teach fluorescence kinetics of MANT-GTP plotted verses time on Figs.6 and 7 of on page 13775. Rammer et al show that hydrolysis of MANT-GTP results in decreased fluorescence. However Rammer et al do not teach the effect of a compound on nucleotide cyclases wherein the cyclases comprises a receptor linked extra-cellular ligand binding domains and intracellular nucleotide cyclase domain or an intracellular domain such as the NO-activated guanylyl cyclase. Holtwick et al teach guanylyl cyclase-A receptors expressed in a wide variety of tissues that are important in the mechanism of vascular tone. Applicants invention comprises a fluorescent based method for screening test compounds for their effect on membrane bound nucleotide cyclases wherein the cyclases may comprise a receptor linked extra-cellular ligand binding domains and intracellular nucleotide cyclase domain (guanylyl cyclase-A) or an intracellular domain such as the NO-activated guanylyl cyclase by utilizing fluorescent nucleotide analogues. The difference between the method used by Rammer et al is that Rammer et al's method is drawn to the use of a fluorescent nucleotide analog to study G protein activation in the presence or absence of a compound while applicant's method is drawn to a method of screening for a test compound that modulates a nucleotide cyclase using a fluorescent nucleotide analog. Thus it would have been obvious for a person of ordinary skill in the art who possess the knowledge of the use of a fluorescent nucleotide analog in the study of a compound that modulates a G protein (as taught by Rammer et al) to use the fluorescent nucleotide analog to screen for a compound that

modulates a signal transduction protein such as guanylyl cyclase involved in a disease process (as taught by Holtwick et al)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kagnew Gebreyesus PhD.

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